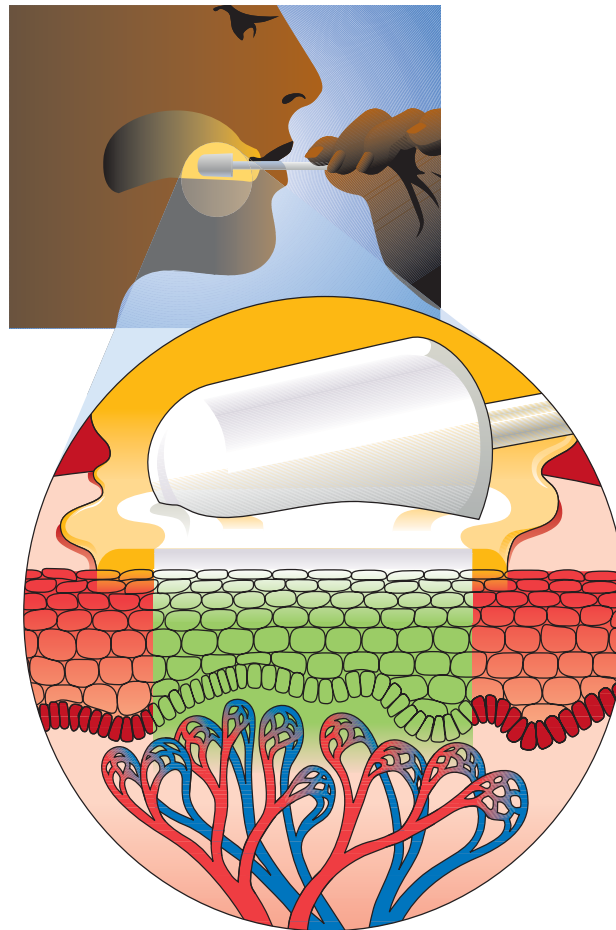


# *Oral Transmucosal Delivery of Fentanyl Citrate for Breakthrough Cancer Pain Relief*



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## **Chapter 1**

### **Title and Executive Summary**

#### ***Oral Transmucosal Delivery of Fentanyl Citrate for Breakthrough Cancer Pain Relief***

#### **Executive Summary**

Episodes of breakthrough cancer pain are relatively common occurrences for patients undergoing cancer treatments. Characterized by pain unrestrained by traditional medications, these physical burdens impose a significant degree of suffering. In order to control and eliminate this pain, Actiq, a pharmaceutical lollipop, has been developed to provide rapid oral transmucosal delivery of fentanyl citrate, a potent medicinal narcotic. To elucidate the pharmacokinetics of the drug under various dosages, a computer model of fentanyl diffusion in the oral cavity was designed in COMSOL. Upon solving the model process, concentration profiles of fentanyl in the mucosa over time were developed for various dosages. Sensitivity analyses were also performed to determine the effects of several parameters on fentanyl diffusion. The resulting concentration profiles showed that peak concentrations of  $0.00079 \text{ g/m}^3$ ,  $0.0016 \text{ g/m}^3$ , and  $0.0032 \text{ g/m}^3$  for 200  $\mu\text{g}$ , 400  $\mu\text{g}$ , and 800  $\mu\text{g}$  dosages, respectively, were achieved at approximately 800 seconds. Additionally, based upon the sensitivity analyses, the fentanyl solubility and the lollipop radial dissolution rate have the greatest impact on fentanyl concentration and diffusion. Future research can be performed to optimize the drug diffusion by altering these two parameters, ultimately yielding a more effective Actiq product.

## Chapter 2

### Introduction and Design Objectives

#### 2.1 Introduction

A painkiller in the form of a lollipop, Actiq provides almost instant pain relief for cancer patients undergoing chemotherapy, especially those experiencing breakthrough pain. This pain is unhampered by conventional medications, such as morphine, and causes considerable distress for patients. Within the Actiq product itself, the active ingredient, fentanyl citrate (see Figure 1), is combined with dissolution agents and compounds to form a solid matrix that dissolves when placed in the oral cavity, subsequently diffusing into the mucosa. In doing so, Actiq enables narcotic pain medication to quickly enter the bloodstream, thereby allowing for fast relief. Numerous fentanyl dosages are currently available, ranging from 200  $\mu\text{g}$  to 1600  $\mu\text{g}$  per lollipop<sup>1</sup>.

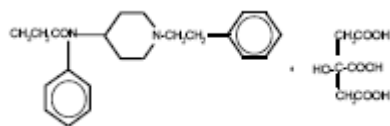


Figure 1. Fentanyl Citrate<sup>2</sup>.

#### 2.2 Problem Schematic

A diagrammatic view of the overall drug delivery system is provided in Figure 3. The lollipop-like solid has a spherical shape, and, since the local environment within the oral cavity is largely aqueous due to the presence of saliva, a layer of saliva surrounds the lollipop. This complex is further surrounded by the oral mucosa (Figure 2); the specific tissue layer of interest within the mucosa is the buccal epithelium. Since the solid is positioned at the inside corner (cheek) of the oral cavity, the mucosa can be modeled as engulfing the spherical lollipop (Figure 3). Consequently, as the drug-containing lollipop solid dissolves within the oral cavity, fentanyl citrate is released and diffuses through the salivary and oral mucosa epithelial layers.

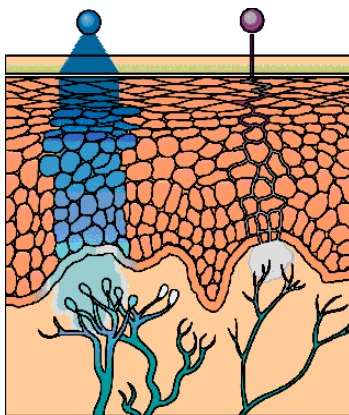
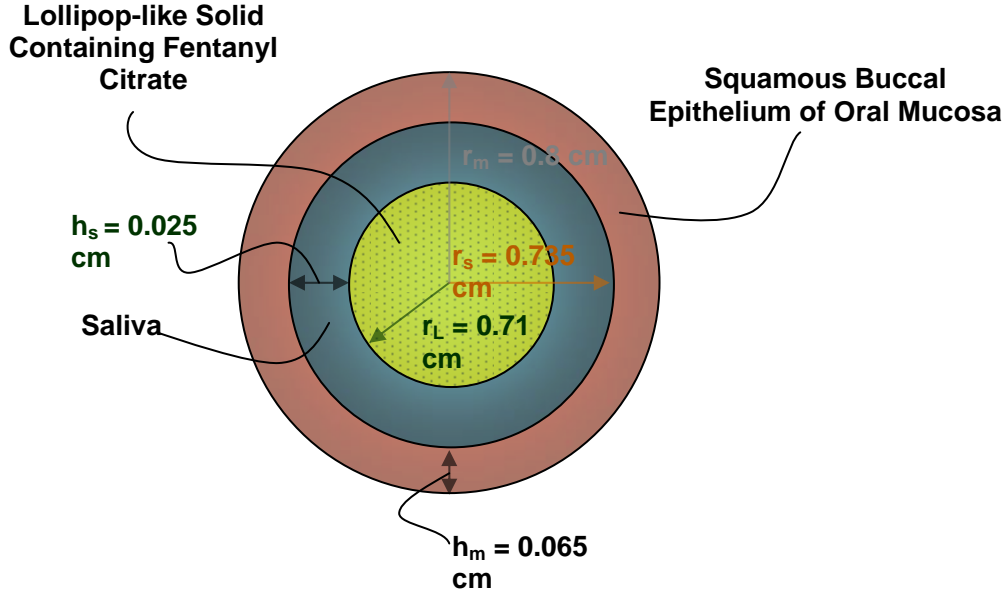
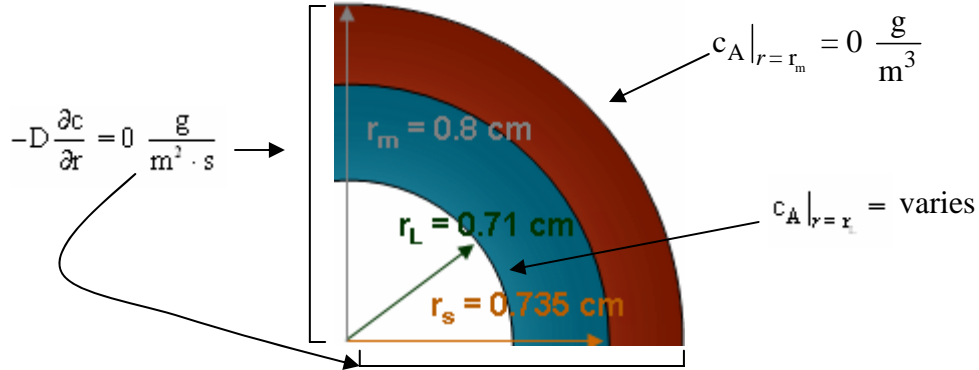


Figure 2. Oral Mucosal Membrane<sup>1</sup>.



**Figure 3. a) Schematic (cross-section) of oral transmucosal fentanyl citrate delivery system with dimensions.** Note that the figure is not drawn to scale, and the value provided for  $r_L$  is an initial value (see below for more details).



**b) Schematic of quarter-circle that is utilized to model the system in COMSOL.** Note that the lollipop itself is not considered in COMSOL; diffusion is modeled solely through the saliva and mucosa. Boundary conditions are also provided.

As the lollipop dissolves within the oral cavity, the pressure exerted by the cheek of the patient forces the mucosa and saliva inward towards the lollipop. As such, the thickness of the mucosa and saliva remain constant as the lollipop dissolves; however, the radius of the lollipop,  $r_L$ , decreases (see Appendices A and C for further details).

## 2.3 Design Objectives

Central to each medicinal lollipop's design is how the drug dissolves and enters the bloodstream via the mucosa. However, the pharmacokinetic effects of fentanyl citrate within the mucosa during oral transmucosal delivery have not yet been evaluated. By modeling the diffusion of fentanyl in the oral cavity, mucosal concentration profiles over time can be developed for specific doses. Comparison of these profiles would provide valuable information

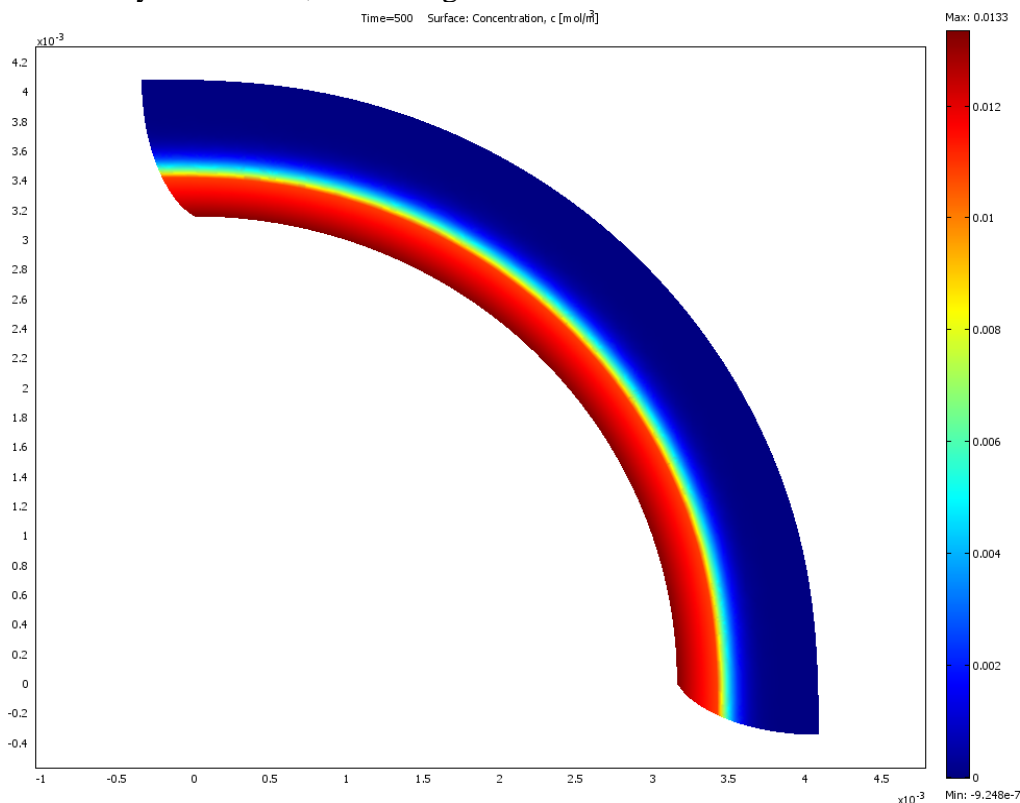
regarding the pharmacokinetic variations of fentanyl among different doses (200  $\mu\text{g}$ , 400  $\mu\text{g}$ , and 800  $\mu\text{g}$ ).

The ensuing report includes a discussion of the results of the simulation, followed by design recommendations and other conclusions.

## Chapter 3 Results and Discussion

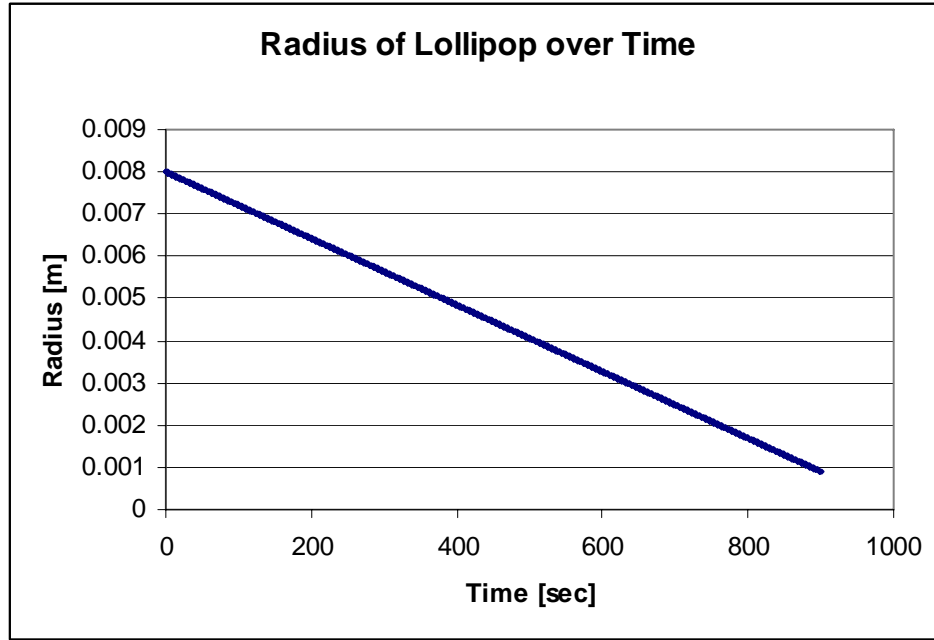
### 3.1 Complete Solution

Using a time step of 0.5 seconds over a period of 900 seconds (average usage time), the following surface contour plot was generated (Figure 4), affording additional insight to the physical situation. At the interface of the saliva and mucosal membrane, the concentration of fentanyl citrate is at a maximum of  $0.0133 \text{ g/m}^3$ . The initial concentration of fentanyl citrate within the Actiq lollipop is  $266.67 \text{ g/m}^3$ . This large decrease in concentration over the layer of saliva is attributed to the degradation of fentanyl citrate within the saliva, which represents the amount of drug lost due to swallowing. In clinical trials, almost seventy-five percent of the drug is lost in the saliva as the patient swallows and thus, does not enter the mucosal membrane. To account for this loss, the model included a sink term in the saliva, in which fentanyl citrate is specified to have a degradation rate of seventy-five percent. In addition, there is also a gradual decrease in concentration as the drug moves through the mucosal membrane. As the outer boundary of the mucosal membrane is approached, the concentration of fentanyl citrate decreases to zero, as described by the prescribed boundary condition,  $c(r = 0.008 \text{ m}) = 0 \text{ g/m}^3$ . Also, in order to account for the radial dissolution of the lollipop, the overall mesh was implemented as a dynamic mesh, decreasing in radius at a rate of  $7.8889 \times 10^{-6} \text{ m/sec}$ .



**Figure 4. Surface plot at 500 seconds.** Color gradations indicate fentanyl citrate concentration.

Since the model takes into account the dissolution, and thus the changing radius, of the lollipop, a rate of change was specified. In Figure 5, the change in the radius of the lollipop over time is shown. Note the 900 second period – since patients used the lollipop over an average of fifteen minutes, all analyses were made over that specified time. As noted in the figure and suggested by the linear plot, the lollipop radius decreases at a constant rate. This is consistent with the  $r_L(t)$  equation previously derived.

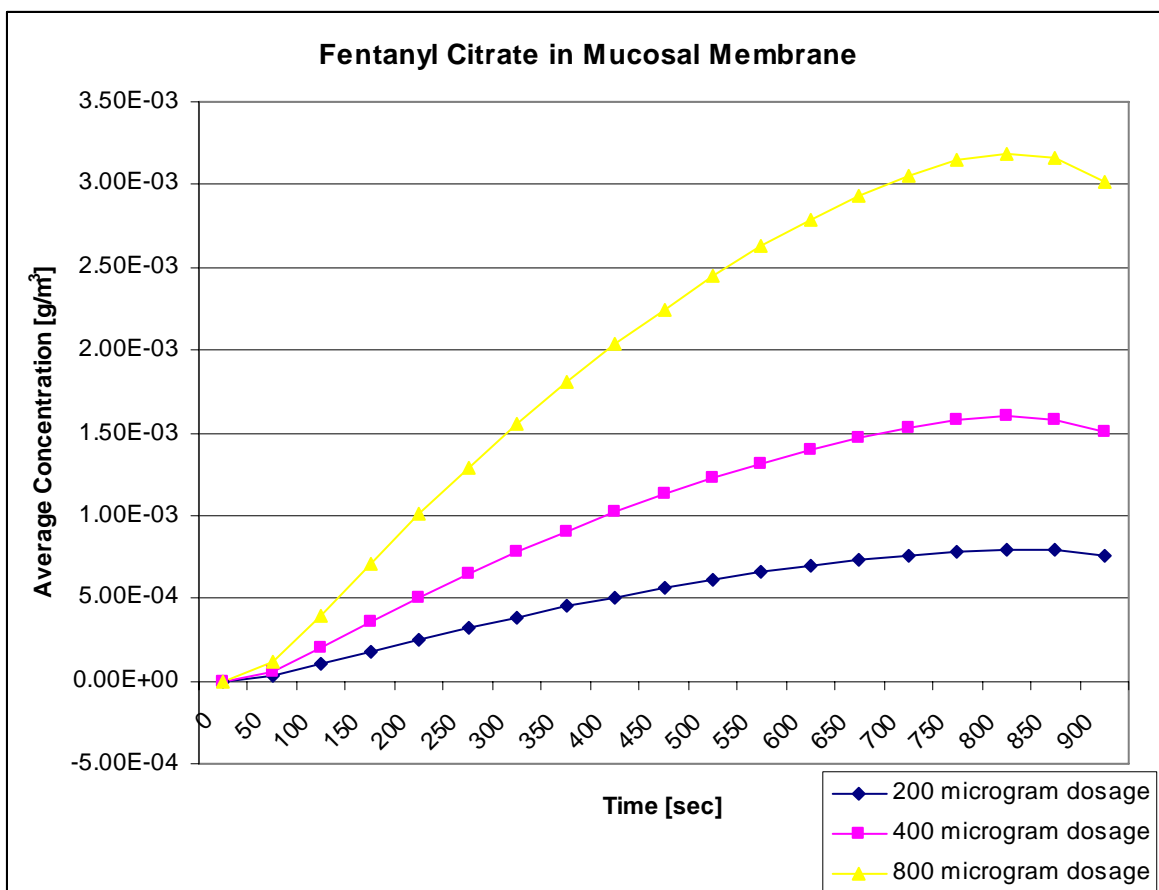


**Figure 5. Plot of lollipop radius over time.** The linear fashion in which the radius decreases indicates a constant rate of change.

To evaluate the various doses, the boundary and initial conditions outlined in Appendix A were utilized. The conditions were the same for all doses, except for the concentration boundary condition at  $r_L$ , which varied depending upon the fentanyl dosage. As for physical properties, the diffusivities of each layer were defined. The diffusivity of fentanyl through the saliva was found to be  $2.2603 \times 10^{-10} \text{ m}^2/\text{sec}$ , and the diffusivity through the mucosa is  $1.548 \times 10^{-11} \text{ m}^2/\text{sec}$ .

### 3.2 Dosage Concentration

The average concentration of fentanyl citrate over time in the mucosal membrane was also analyzed for three different dosages to give further insight into drug's diffusion mechanism. Figure 6 shows the average concentration over time for a 200, 400 and 800  $\mu\text{g}$  dosage, respectively. All other variables, subdomain properties and boundary properties remained the same. Note that the concentration profiles for all initial dosages reflect the same trend: the average concentration increases linearly until it reaches a peak and then decreases. Interestingly, the peak is reached at 800 seconds into the treatment for all dosages. As expected, the maximum average concentration will be varied for each dosage. The highest dosage, 800  $\mu\text{g}$ , resulted in a maximum average concentration of  $0.0032 \text{ g/m}^3$  while the lowest dosage, 200  $\mu\text{g}$ , resulted in a maximum average concentration of  $0.00079 \text{ g/m}^3$ . Physically, these findings make sense. If the lollipop begins with a higher concentration, then the same layer will have a higher amount of drug in the same amount of time than when the lollipop began with a lower concentration.



**Figure 6. Concentration Profile with 200  $\mu\text{g}$ , 400  $\mu\text{g}$  and 800  $\mu\text{g}$  dosage.** The peak average concentration is reached around 800 seconds.

### 3.3 Sensitivity Analysis

Since most of the property values in this model were experimental properties, a sensitivity analysis was crucial in evaluating the solution's sensitivity to possible discrepancies in these values. Among the parameters evaluated were the diffusivity of both the saliva and the mucosal membrane, the solubility of the lollipop and the radial rate of change over time. These values were changed to the values listed in Table 1. Only one parameter was changed at one time to ensure that deviations from the original solution were solely due to that particular parameter.

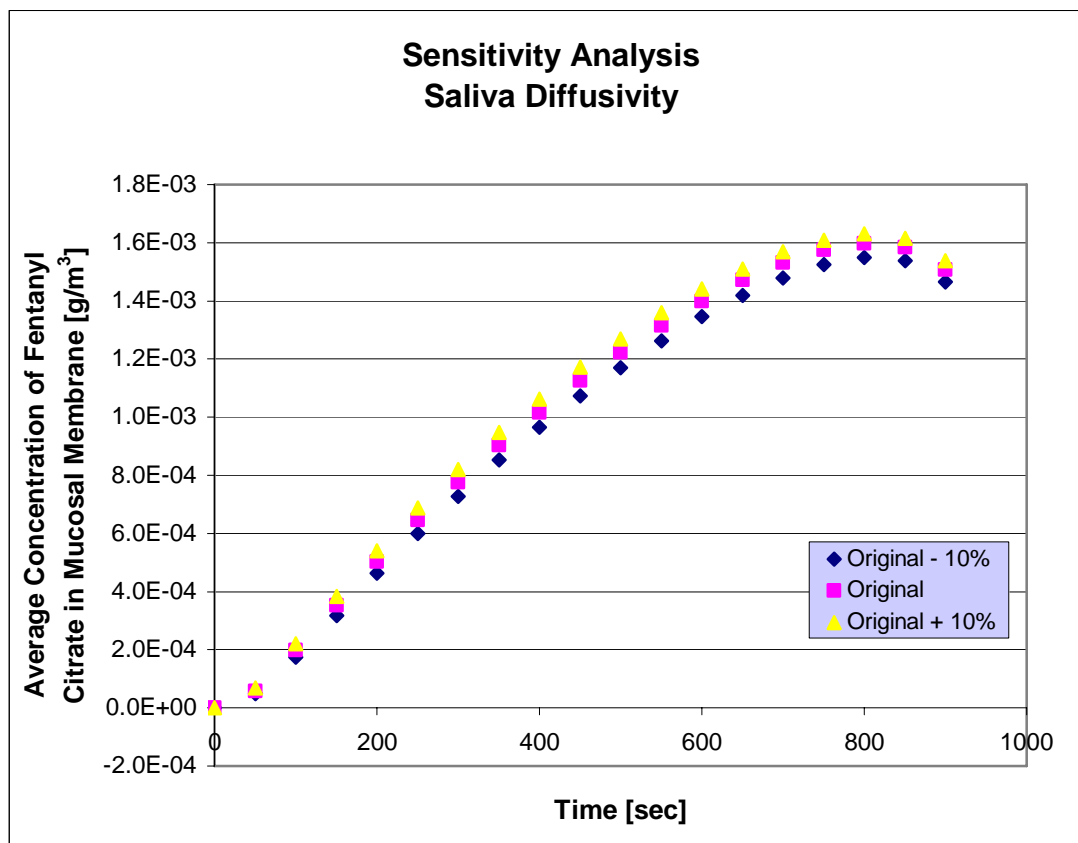
**Table 1. Values used for sensitivity analysis.** Values deviated from the original values by ten percent.

Parameters	Original - 10%	Original	Original + 10%
Diffusivity (saliva; $\text{m}^2/\text{sec}$ )	2.0343E-10	2.2603E-10	2.4863E-10
Diffusivity (mucosal membrane; $\text{m}^2/\text{sec}$ )	1.393E-11	1.548E-11	1.703E-11
Solubility	0.00018	0.0002	0.00022
$dr/dt$ (m/sec)	7.1000E-06	7.8889E-06	8.6778E-06



### 3.3.1 Diffusivity of Fentanyl Citrate in Saliva

When analyzing the model's sensitivity to the saliva diffusivity, the new solutions still followed a trend similar to the original solution. According to Figure 7, the average concentration of the drug steadily increased in the mucosal membrane and reached a peak at around 800 seconds after the initial administration of the lollipop. Moreover, as expected, a decrease in diffusivity resulted in a smaller maximum average concentration since less of the drug was able to diffuse into the saliva, and subsequently into the mucosal membrane, over time. An increase in saliva diffusivity produced the opposite effect, as expected as well. The peak's value (the maximum average concentration), however, was different for each case. Using a saliva diffusivity 10% less than the original, the maximum average concentration was approximately  $1.548 \times 10^{-3} \text{ g/m}^3$ . This value is about three percent less than the maximum average concentration obtained with the original saliva diffusivity value. On the other hand, using a saliva diffusivity 10% more than the original yielded a maximum average concentration of  $1.63 \times 10^{-3} \text{ g/m}^3$ , two percent greater than that obtained with the original. These changes, however, are quite small and expected. Thus, the model does not seem to be too sensitive to changes in the diffusivity of fentanyl citrate in the saliva.



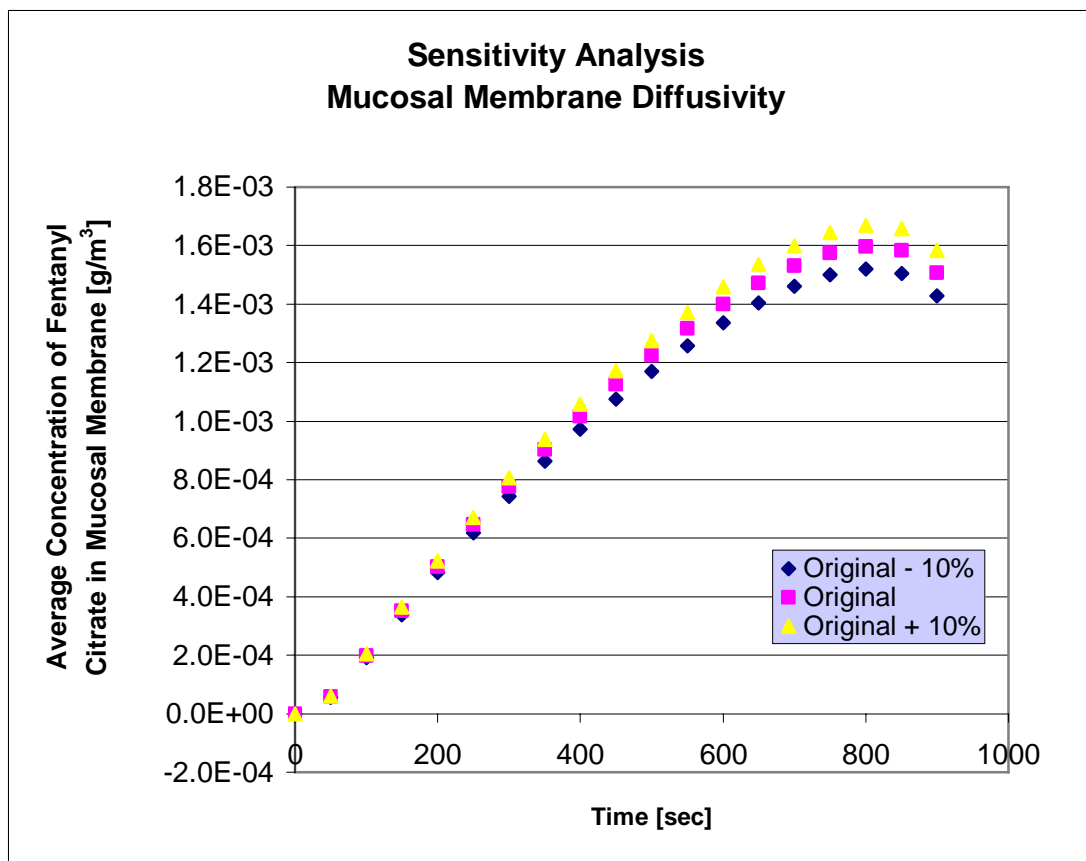
**Figure 7. Sensitivity Analysis with Varying Saliva Diffusivity.** The dosage utilized for this analysis was 400  $\mu\text{g}$ .

### 3.3.2 Diffusivity of Fentanyl Citrate in Mucosal Membrane

Another parameter tested in the sensitivity analysis was the mass diffusivity in the mucosal membrane. By increasing and decreasing the mass diffusivity by 10% in this subdomain, the average concentrations of the drug over time were plotted for each different

diffusivity. The maximum average concentrations obtained with the new diffusivities (Figure 8) were then compared with those obtained with the original diffusivity ( $1.548 \times 10^{-11} \text{ m}^2/\text{s}$ ). As seen from the graphs below, all maximum average concentrations of the drug in the mucosal membrane peaked at the same time (about 800s). Also, as expected, an increase in mass diffusivity coefficient resulted in an increase in concentration in the mucosal membrane because more of the drug was able to diffuse into the membrane during a given amount of time. Conversely, a decrease in mass diffusivity would indicate that less drug is diffused through the membrane over time.

The concentrations, however, peaked at different maximum values. With a 10% increase in mass diffusivity (a value of  $D = 1.703 \times 10^{-11} \text{ m}^2/\text{s}$ ), the maximum average concentration of the drug at 800 seconds was  $1.67 \times 10^{-3} \text{ g/m}^3$ , about 4.5% increase from the maximum average concentration of the drug also at 800s but with the original mass diffusivity coefficient. Similarly, with a 10% decrease in mass diffusivity (a value of  $D = 1.393 \times 10^{-11} \text{ m}^2/\text{s}$ ), the maximum average concentration of the drug at 800 seconds was  $1.519 \times 10^{-3} \text{ g/m}^3$ , a 4.8% decrease from the maximum average concentration of the drug with the original mass diffusivity in the mucosal membrane.

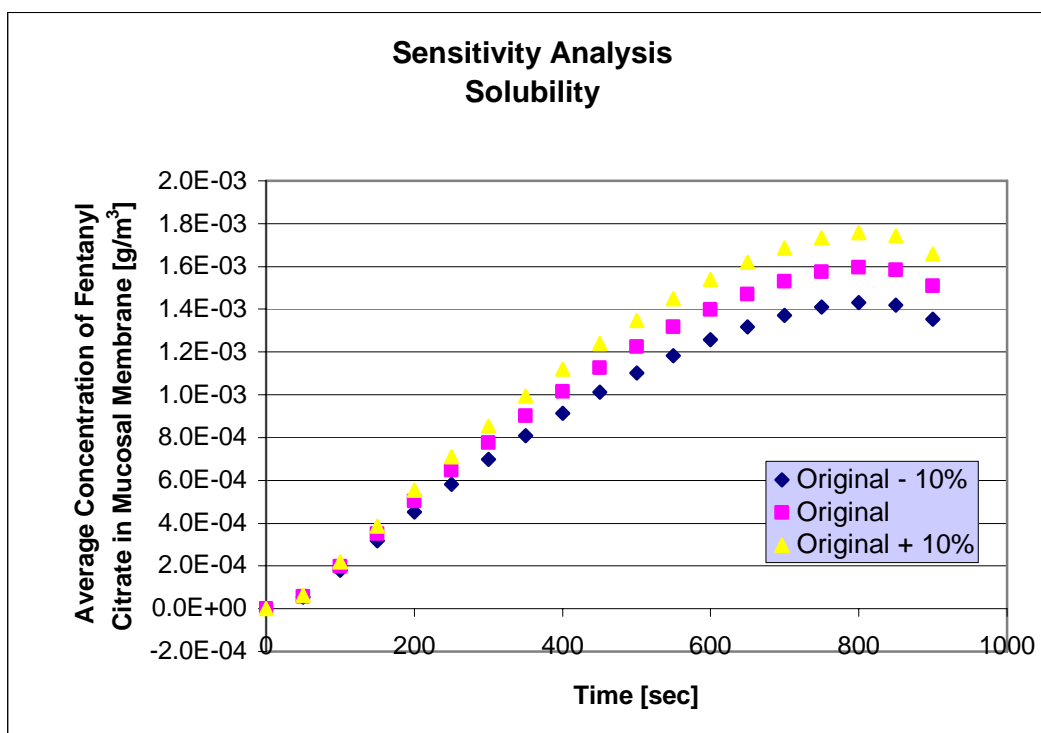


**Figure 8. Sensitivity Analysis with Varying Mucosal Membrane Diffusivity.** The dosage utilized for this analysis was 400  $\mu\text{g}$ .

### 3.3.3 Solubility

The variation in solubility follows a similar trend to other parameter variations (Figure 9). There is a nearly linear increase in the average concentration of fentanyl citrate in the mucosal

membrane. Solubility of the mucosal membrane was varied positively and negatively by 10% to determine the model's sensitivity to the parameter. All three plots (-10%, 0%, +10% change) exhibited peaks at approximately 800 seconds. A -10% change in concentration resulted in a peak average concentration of  $1.43 \times 10^{-3} \text{ g/m}^3$ , about ten percent less than the original peak average concentration. The original plot resulted in a peak of  $1.60 \times 10^{-3} \text{ g/m}^3$ . When solubility was increased by 10%, the peak average concentration reached  $1.76 \times 10^{-3} \text{ g/m}^3$ , also about ten percent less than the original peak average concentration. This result is intuitive because the solubility of the mucosa to fentanyl citrate was positively correlated to peak average concentration. This observation also suggests a linear relationship between solubility and average peak concentration.



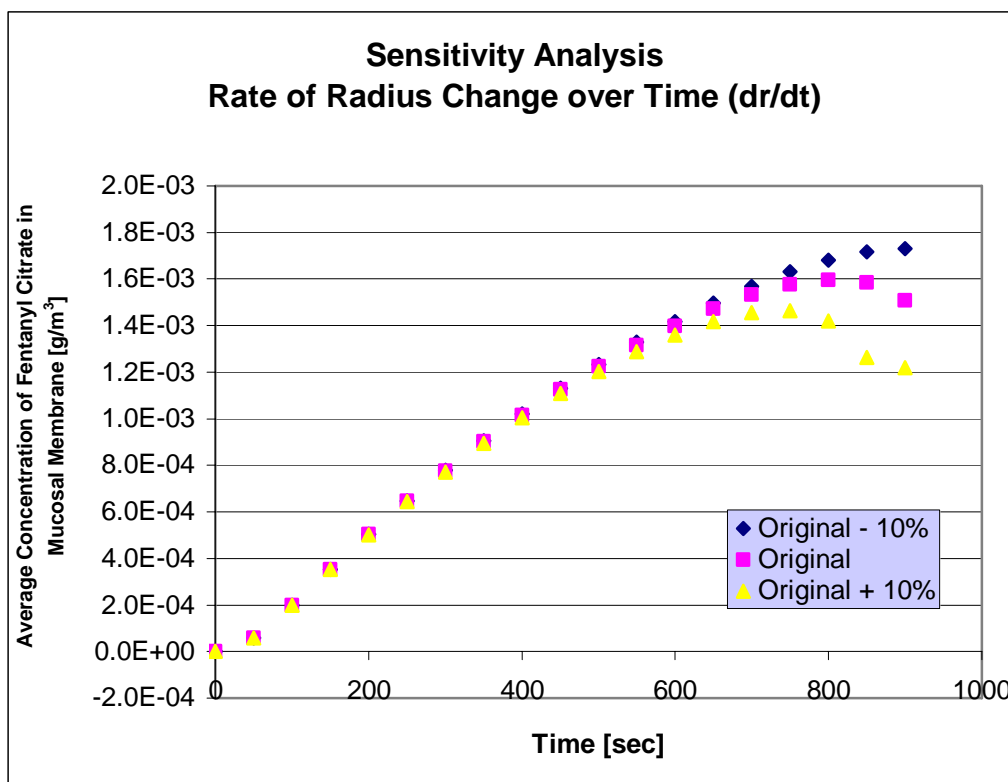
**Figure 9. Sensitivity Analysis with Varying Solubility.** The dosage utilized for this analysis was 400  $\mu\text{g}$ .

### 3.3.4 Radial Dissolution Rate

As noted in Figure 10, the plots all follow the same general trend: a fairly linear (slightly curved) increase from 0 sec to approximately 700 sec, at which point the plots begin to curve as they attain peak values. Such a trend is consistent with the physical situation. As the lollipop dissolves, it serves as a fairly steady source of fentanyl for the oral cavity, represented by a nearly linear increase in fentanyl concentration over time. As the lollipop reaches an almost completely dissolved state, however, the amount of fentanyl released begins to drop. Consequently, the concentration within the oral cavity, including the mucosa, decreases; this is evidenced by the curving of the plots.

All three plots, although characterized by the same overall form, display slight differences. Perhaps the most notable deviation is the differing peak average concentration values. For the 10% *lower* radial dissolution rate ( $dr/dt = 7.1 \times 10^{-6} \text{ m/sec}$ ), the peak concentration

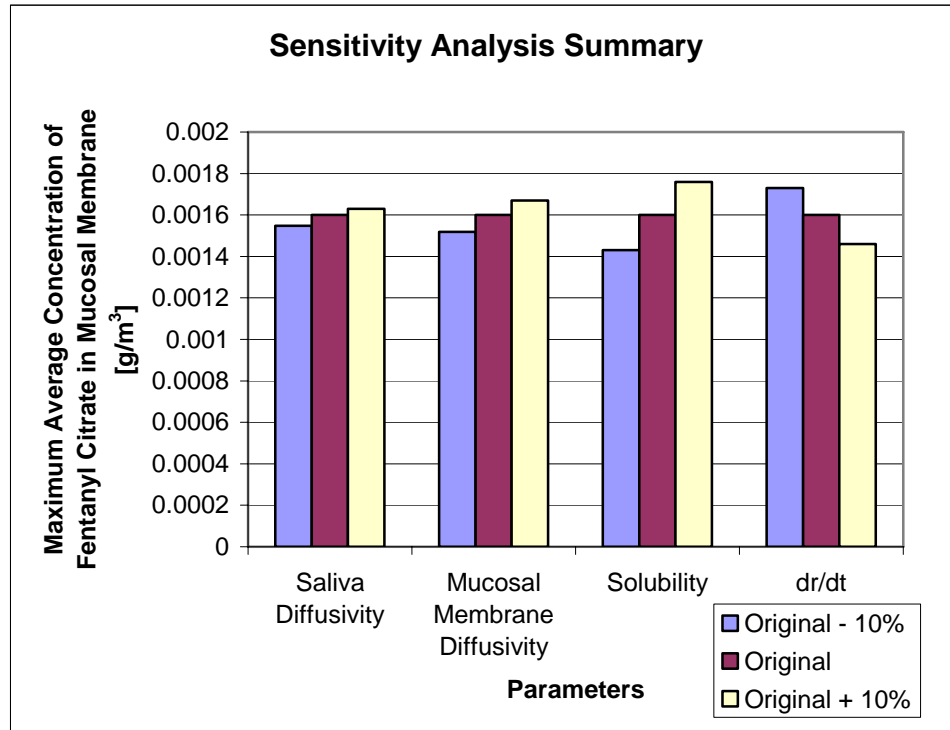
was  $1.73 \times 10^{-3} \text{ g/m}^3$ , while the peak concentration for the 10% *higher* radial dissolution rate ( $dr/dt = 8.6778 \times 10^{-6} \text{ m/sec}$ ) was  $1.46 \times 10^{-3} \text{ g/m}^3$ . Considering the peak concentration of the original radial dissolution rate ( $dr/dt = 7.8889 \times 10^{-6} \text{ m/sec}$ ) of  $1.60 \times 10^{-3} \text{ g/m}^3$ , these peak values each represent an 8.3% deviation from the original peak; the lower  $dr/dt$  value corresponded to a higher peak concentration, whereas the higher  $dr/dt$  value corresponded to a lower peak concentration. This comparison yields an inverse trend between radial dissolution rate and peak concentration. The same trend is evident when comparing the time to attain the peak value. The times at which the peak concentration was attained were  $t = 900 \text{ sec}$  (a 12.5% increase over the original) for the lower  $dr/dt$  condition,  $t = 800 \text{ sec}$  for the original, and  $t = 750 \text{ sec}$  (a 6.25% decrease over the original) for the higher  $dr/dt$  condition. Overall, the stated variations in the values and times of the peak concentration indicate that the modeling system is slightly sensitive to changes in the radial dissolution rate. Therefore, it is advisable to input an accurate radial dissolution rate value since inaccuracies could lead to variations, albeit slight, in peak values and times when attempting to analyze the diffusion process.



**Figure 10. Sensitivity Analysis with Varying  $dr/dt$ .** The dosage utilized for this analysis was  $400 \mu\text{g}$ .

### 3.3.5 Summary

Changes in maximum concentration of fentanyl citrate due to subsequent changes in the four parameters are summarized in Figure 11. A brief glance reveals that solubility and the radial rate of change over time both gave the most significant changes in the solution while both diffusivities gave the least. While all models should utilize the most accurate data possible, special care should be taken in obtaining accurate solubility and radial rate of change values.



**Figure 11. Summary of sensitivity analysis results.** Diffusivities did not influence the solution of the model as much as solubility and radial rate of change.

## **Chapter 4**

### **Conclusion and Design Recommendations**

From our model and subsequent sensitivity analyses, the oral transmucosal delivery of fentanyl citrate at all three dosages can effectively deliver the drug within the proposed time. Changes in the solubility and dissolution rate affect the greatest change in the analysis, as seen in Figure 11, and so, great care must be taken when these values are derived. Thus, the model's sensitivity to the solubility and dissolution rate suggest that further optimization of the model would benefit from investigating changes in these variables. Focusing the optimization on the other two variables, diffusivities of fentanyl citrate in saliva and mucosal layers, would not be as beneficial since the model is not as sensitive to such changes. For example, if we were to minimize the amount of time necessary for effective drug delivery, the solubility and dissolution rate should be changed, either by changing the combination of emulsifiers or stabilizers (dissolution agents) in the lollipop, such that more of the drug arrives in the mucosal layer in a shorter amount of time. Additional laboratory experimentation is necessary to determine the specific values of these parameters.

It has been shown that the oral transmucosal delivery of fentanyl citrate is able to deliver effective concentrations to the blood for breakthrough cancer pain relief. However, this result alone does not explain the efficacy of the delivery method. The ease of application in conjunction with its reliability explains why oral transmucosal delivery is the best method for the treatment of breakthrough cancer pain. While intravenous (IV) delivery of fentanyl citrate accounts for the highest blood concentration of drug, IV is not a feasible method for self-application in cancer patients. A patient enduring breakthrough pain will not be capable of administering an IV. Conversely, the other form of oral drug delivery is the ingestion of a pill or liquid. While oral ingestion of fentanyl provides a relatively easy method of drug delivery, the concentration fentanyl in the blood can not attain the same levels as in oral transmucosal delivery in the same amount of time. Oral ingestion requires the drug to be taken into the digestive tract, prior to the nervous system. Oral transmucosal delivery does not have this requirement, making oral transmucosal delivery of fentanyl citrate the form of administration that will produce the best overall effect for the patient. The tradeoffs made between maximum drug concentration and ease of delivery is at a level that makes this delivery vessel the most effective for individual breakthrough pain management.

#### ***Social Issues***

Fentanyl citrate, as an analgesic, is a highly potent opiate-based narcotic. The magnitude of its potency is reflected in the fact that fentanyl is 80 times more powerful than morphine. As such, if used by people who are non-opiate tolerant, a standard dose of fentanyl can lead to a rapid overdose. Given that it is such a strong narcotic, fentanyl has the potential to be insidiously addictive, and is thus prone to abuse. Its illegal use began in 1979 during a horse race in which fentanyl was used as a stimulant to enhance racing performance. The illegal applications have since broadened, including the use of fentanyl to subdue criminals and rebels. Fentanyl has also developed a presence in illicit drug sales, where its Actiq formulation is referred to as "percipop" and is sold to opiate addicts. Ultimately, the multitude of fentanyl derivatives and analogues, such as sufentanil, carfentanil, and alfentanil, enable the narcotic to be distributed in a variety of media. In this way, the drug's accessibility transforms it into a prime target for abuse.

Given these circumstances, it is clear that restrictions should be placed on fentanyl usage and availability in order to mitigate the social consequences of its abuse. Such restrictions would likely be manifest in more rigid laws and stricter regulations on how fentanyl-based products and pharmaceuticals are handled in hospitals. Additionally, further enhancements to the Actiq formulation, such as those proposed by the design recommendations, should be implemented with care given the drug's potential for abuse. Changing the solubility and radial dissolution rate of the lollipop would enhance its effectiveness in relieving pain without making fentanyl much more readily available. However, while improvements would certainly aid individuals seeking breakthrough cancer pain treatment, any changes should be made with drug abuse in mind.

### ***Health and Safety***

Actiq was first issued its FDA approval on November 11, 1997<sup>1</sup>. Although the drug may seem beneficial to the cancer patient who experiences excruciating breakthrough pain, the drug may propose some dangers to the patient and especially those who cannot tolerate opioid treatment, such as children. Because small children have the tendency to put things in their mouth, especially when the object has a pleasurable taste, the potential for accidental child poisoning increases. According to the Warning label on the actual drug, small units of the drug contain enough medicine to be fatal to a child<sup>2</sup>. Side effects include hallucination, abnormal muscle contractions, seizures and lastly respiratory depression, the ultimate cause of death<sup>3</sup>. A recent study at Jefferson Medical College in Pennsylvania showed that doses greater than 15 µg/kg administered to children under 6 years old led to post-operative nausea, vomiting and occasional respiratory depression<sup>4</sup>. Thus leaving the drug unattended and into the hands of a child may become an execrable event.

As a solution, the producers of Actiq supply the drug in “individual child-resistant blistered packages.” Unfortunately these childproof bags do not prevent children from accessing the drug when the drug is out of the package. Thus, the producers also supply the patient with a temporary storage unit, called “ACTIQ Welcome Kit”, which resembles a bottle with a cap on it<sup>2</sup>. The unit is meant for patients who cannot finish the lollipop in time or wish to hold the lollipop in a safe and secure way. This storage also prevents children from gaining access to the deadly painkiller. Unfortunately, the safety packaging may not be enough. Since the launch in 1997, two child deaths have already been reported after accidental poisoning.<sup>5</sup>

Another ethical issue at hand is Actiq being prescribed by doctors to patients who are experiencing pain but not as severe as cancer breakthrough pain. By FDA criterion, patient can only be prescribed for Actiq if he/she has already been taking pain medication for chronic cancer pain and is experiencing severe spikes in pain. According to a report in PR Newswire in 2005, a study showed that only 10 percent of the patients receiving the drug were patients prescribed for breakthrough cancer pain while the other 90 percent were “off-label,” or not prescribed according to the FDA guidelines set forth by FDA<sup>5</sup>. The study also showed that more than 15 percent of Actiq prescriptions were for more than the FDA's recommended 120 lollipops per month, suggesting that some patients may be overusing the drug<sup>6</sup>.

Thus, it is pertinent that doctors prescribe Actiq to patients who essentially require the drug to control their breakthrough pain and who have a low risk of exposing the drug to non-users. This will prevent the possibility of drug abuse and allowing the drug to fall into the wrong hands.

## Chapter 5

### Appendices

#### 5.1 Appendix A

Assuming only radial diffusion through the spherical geometry and drug delivery due to transient diffusion, the mass transport equation, in spherical coordinates, simplifies to:

$$\frac{\partial c_A}{\partial t} = \left( \frac{D}{r^2} \right) \left[ \frac{\partial}{\partial r} \left( r^2 \frac{\partial c_A}{\partial r} \right) \right]$$

, where “A” refers to fentanyl citrate.

The reaction term is accounted for in the boundary conditions, and is thus not included in the above governing equation. Such a reaction term is necessary to explain the amount of drug lost due to swallowing.

Assuming a constant radial dissolution rate of the lollipop radius, the following equation was derived to describe the lollipop radius as a function of time (See Appendix C for derivation.):

$$r_L = (-7.8889 \times 10^{-6} \text{ m/sec})(t) + r_0, \text{ where } r_0 = \text{initial lollipop radius.}$$

#### *Boundary Condition Calculations*

Actiq is available in a variety of doses, ranging from 200 µg to 1600 µg. The 200, 400, and 800 µg dosages, however, are prescribed most often and thus, these dosages were utilized for the complex solution analysis.

The volume of the lollipop is equal to 1.5 cm<sup>3</sup>, or 1.5 x 10<sup>-6</sup> m<sup>3</sup>. At the lollipop's outermost boundary (the lollipop-saliva interface), the concentration of the active ingredient, fentanyl citrate, is assumed to be constant. In order to account for the solubility of the fentanyl as well as the diffusive reaction term, however, two additional terms were determined:

- i. Solubility = 0.0002
- ii. Typically, 75% of the fentanyl is eliminated through swallowing, greatly reducing the analgesic effectiveness of fentanyl by leaving only 25% to diffuse through the saliva and mucosa. Therefore, the concentration exiting the lollipop is scaled by a factor of 0.25.

Compiling these terms, the concentration at  $r_L$  was calculated as follows:



$$c_A|_{r=r_L} = \left( \frac{\text{Mass}}{\text{Volume}} \right) (\text{Solubility}) \left( \frac{\text{Reaction/Elimination}}{\text{Factor}} \right)$$

, where Mass = mass of fentanyl citrate in one lollipop and Volume = volume of one lollipop.

The fentanyl concentrations for each of the specified dosages were determined utilizing the above equation:

$$\text{For } 200 \mu\text{g Dosage: } c_A|_{r=r_L} = \left( \frac{200 \times 10^{-6} \text{ g}}{1.5 \times 10^{-6} \text{ m}^3} \right) (0.0002)(0.25) = 0.00667 \frac{\text{g}}{\text{m}^3}$$

$$\text{For } 400 \mu\text{g Dosage: } c_A|_{r=r_L} = \left( \frac{400 \times 10^{-6} \text{ g}}{1.5 \times 10^{-6} \text{ m}^3} \right) (0.0002)(0.25) = 0.01333 \frac{\text{g}}{\text{m}^3}$$

$$\text{For } 800 \mu\text{g Dosage: } c_A|_{r=r_L} = \left( \frac{800 \times 10^{-6} \text{ g}}{1.5 \times 10^{-6} \text{ m}^3} \right) (0.0002)(0.25) = 0.02667 \frac{\text{g}}{\text{m}^3}$$

**Boundary Conditions:**

i. Assuming a homogenous mixture of fentanyl within the lollipop, the concentration at the outer edge of the lollipop,  $r_L$ , is constant. Since three different fentanyl dosages are utilized for the analysis, the concentration boundary condition takes on three values. These terms account for reactions with fentanyl, as well as fentanyl solubility:

$$\text{For } 200 \mu\text{g Dosage: } c_A|_{r=r_L} = 0.00667 \frac{\text{g}}{\text{m}^3}$$

$$\text{For } 400 \mu\text{g Dosage: } c_A|_{r=r_L} = 0.01333 \frac{\text{g}}{\text{m}^3}$$

$$\text{For } 800 \mu\text{g Dosage: } c_A|_{r=r_L} = 0.02667 \frac{\text{g}}{\text{m}^3}$$

ii. The concentration of fentanyl citrate in the outer edge of the mucosal membrane is equal to 0  $\text{g}/\text{m}^3$  since the drug is carried away in the bloodstream:

$$c_A|_{r=r_m} = 0 \frac{\text{g}}{\text{m}^3}$$

iii. All other boundaries are considered to be insulated and thus have a zero flux:

$$-D \frac{\partial c}{\partial r} = 0 \frac{\text{g}}{\text{m}^2 \cdot \text{s}}$$

These boundary conditions are set as default conditions by the COMSOL software, and therefore are not specified by the user.

**Initial Condition(s):**

i. Since no drug is initially present within the oral cavity or its components, the concentration of fentanyl citrate is equal to  $0 \text{ g/m}^3$  in the saliva and the mucosal membrane at  $t = 0 \text{ sec}$ :

$$c_A(t = 0 \text{ sec})|_{r_L < r \leq r_m} = 0 \frac{\text{g}}{\text{m}^3}$$

Boundary conditions, initial conditions, properties, and other parameters are summarized below in Table A1.

**Table A1. a) Conditions and properties for complete solution.**

Boundary Conditions	Initial Conditions	Properties <sup>9</sup>
$c_A _{r=r_L} = 0.00667 \frac{\text{g}}{\text{m}^3} \text{ (200 } \mu\text{g dose)}$ $c_A _{r=r_L} = 0.01333 \frac{\text{g}}{\text{m}^3} \text{ (400 } \mu\text{g dose)}$ $c_A _{r=r_L} = 0.02667 \frac{\text{g}}{\text{m}^3} \text{ (800 } \mu\text{g dose)}$	$c_A(t = 0 \text{ sec}) _{r_L < r \leq r_s} = 0 \frac{\text{g}}{\text{m}^3}$	$D_{\text{saliva}} = 2.2603 \times 10^{-10} \frac{\text{m}^2}{\text{sec}}$
$c_A _{r=r_m} = 0 \frac{\text{g}}{\text{m}^3}$ $-D \frac{\partial c}{\partial r} = 0 \frac{\text{g}}{\text{m}^2 \cdot \text{s}} \text{ (all other boundaries)}$	$c_A(t = 0 \text{ sec}) _{r_s < r \leq r_s} = 0 \frac{\text{g}}{\text{m}^3}$	$D_{\text{mucosa}} = 1.548 \times 10^{-11} \frac{\text{m}^2}{\text{sec}}$

**b) Dimensions and other input parameters.**

Radius of Lollipop <sup>2</sup>	Thickness of Saliva <sup>8</sup>	Thickness of Mucosa <sup>8</sup>	Solubility <sup>7</sup>	Radial Dissolution Rate
0.0071 m	0.00025 m	0.00065 m	0.0002	$7.8889 \times 10^{-6} \text{ m/sec}$

## 5.2 Appendix B

In order to solve the complete solution, COMSOL software was utilized. The specific linear systems solver was Direct (UMFPACK).

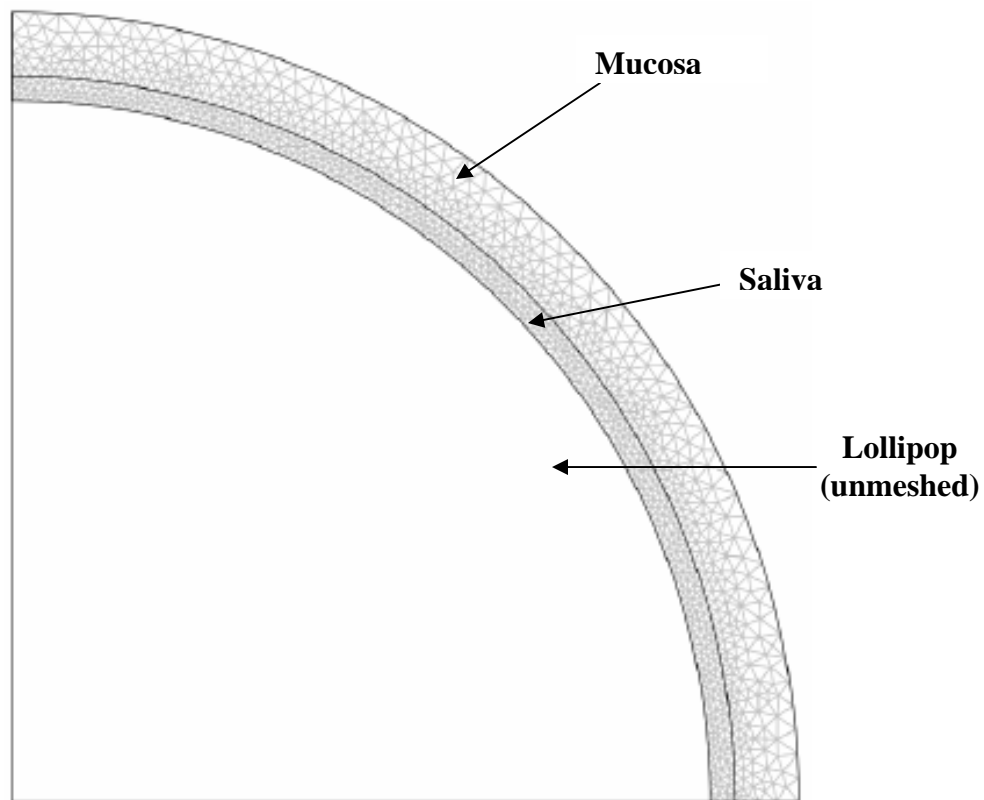
Given that the problem was modeled as transient, calculations were performed from 0 to 900 seconds at a time step of 0.5 seconds.

For the calculations, a relative tolerance of 0.01 was implemented, while an absolute tolerance of 0.0010 was used.

### *Mesh*

For the implementation of the model in COMSOL, 2-D axial symmetry was utilized (since properties, boundary conditions, and overall geometry are symmetric) to construct a quarter circle with two distinct layers. Each layer represented a specific part of the model: the innermost representing the saliva and the outermost layer representing the mucosal membrane. The lollipop, denoted by the *unmeshed* region near the core of the quarter circle, was not integrated into the overall schematic since diffusion was only modeled through the saliva and mucosa layers.

In the complete solution, a maximum element size of 0.0001 was specified for the saliva layer, and a size of 0.00025 was specified for the mucosa layer. This resulted in the mesh found in Figure B1. The mesh consists of triangular elements.



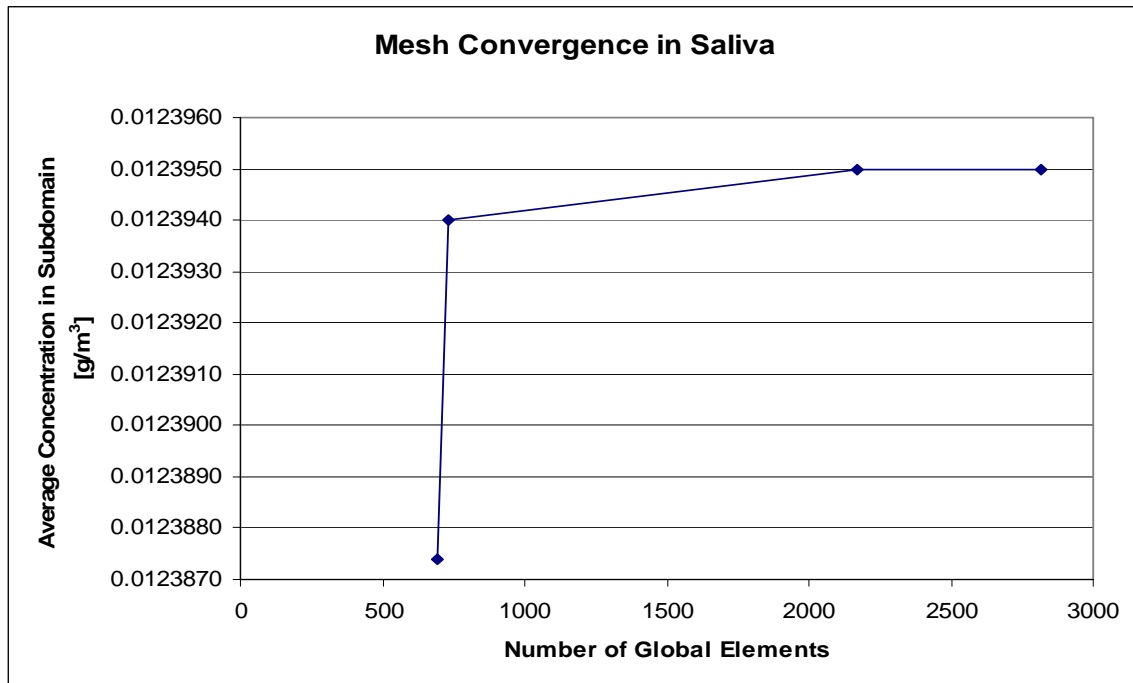
**Figure B1. Mesh for overall schematic.** Note the two distinct physical layers, with the unmeshed lollipop region towards the center.

## Mesh Convergence

A finer mesh was implemented in the saliva layer of our model due to the fact that the majority of the drug diffusion will take place in this layer. Also, the changes in drug concentration over time will be greater in the saliva because of its direct contact with the lollipop and the associated sink term, thus the mesh must consist of more elements than in the mucosal membrane. The mucosal membrane, on the other hand, will have a slightly coarser mesh since the drug concentration will experience significantly less change, compared to the concentration of the drug in the saliva layer.

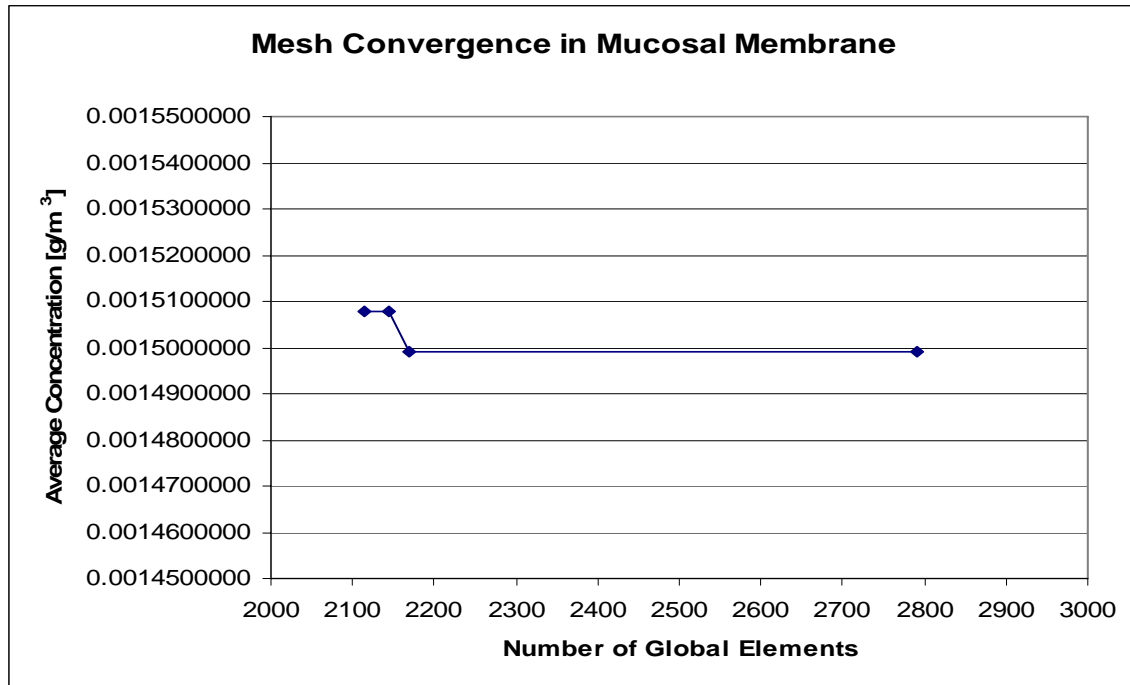
To ensure that the solution was independent of the number of elements, two mesh convergence tests were performed. The meshes for each layer, saliva and mucosal membrane, were varied in maximum element size to determine the minimum number of elements in which the average drug concentration in each layer did not change. Changes in each layer were made separately (i.e. while the maximum element size in the saliva layer was changed, the maximum element size in the mucosal membrane remained constant) so as to ensure that any changes in average concentration were solely due to the variation in that specific subdomain. By choosing the smallest number of elements (and thus, the corresponding maximum element size), the computational time for our model will decrease while still maintaining a high level of accuracy.

According to Figure B2 of the mesh convergence in the saliva layer shown below, the concentration of the drug in the saliva does not change significantly after 2169 global elements. The maximum element size corresponding to this number of global elements is about 0.0001. Thus, the maximum element size of 0.0001 was selected for the saliva layer, since it affords sufficient accuracy for the mesh calculations



**Figure B2. Mesh Convergence in Saliva.** The average drug concentration in the saliva is plotted as a function of number of global elements.

For the mucosal membrane's mesh convergence, the number of elements is slightly different from the saliva layer due to the physics of the model. As shown below in Figure B3, the concentration of the drug in the mucosal membrane does not change significantly after 2169 global elements. The maximum element size corresponding to this number of global elements is 0.00025. Thus, the maximum element size of 0.00025 was selected for the mucosal membrane layer, since it affords sufficient accuracy for the mesh calculations.



**Figure B3. Mesh Convergence in Mucosal Membrane.** The average drug concentration in the mucosal membrane is plotted as a function of number of global elements.

### 5.3 Appendix C

#### *Derivation of $r_L(t)$ Equation for Lollipop Radius*

The spherical geometry of the lollipop, coupled with the conditions within the oral cavity (i.e. saliva encompasses the lollipop uniformly), suggest that the degradation rate of the lollipop radius is uniform throughout the lollipop. Furthermore, given the homogeneity of the lollipop components, the degradation rate can be modeled as constant and approximately equivalent to the average rate. In order to determine the degradation rate, referred to as the radial dissolution rate, the following equation can be employed:

$$\frac{dr_L}{dt} \approx \frac{\Delta r_L}{\Delta t} = \frac{\text{Total Change in Lollipop Radius}}{\text{Total Time of Dissolution}}$$

Given that the lollipop radius is 0.71 cm (0.0071 m) and the total dissolution time, found from literature, is 15 min (900 sec), the radial dissolution rate was calculated as follows<sup>2</sup>:

$$\frac{dr_L}{dt} = \frac{(-)0.0071 \text{ m}}{900 \text{ sec}} = -7.8889 \times 10^{-6} \text{ m/sec}$$

The  $r_L(t)$  equation can be derived from the following integration:

$$\int \frac{dr_L}{dt} \longrightarrow \int_{r_o}^r dr_L = \int_0^t (-7.8889 \times 10^{-6} \text{ m/sec}) dt$$
$$\therefore r_L(t) = (-7.8889 \times 10^{-6} \text{ m/sec})(t) + r_o$$

## 5.4 Appendix D

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